ORIGINAL ARTICLE

Cord Colitis Syndrome in Cord-Blood Stem-Cell Transplantation

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ABSTRACT

BACKGROUND

Diarrhea is a frequent complication of hematopoietic stem-cell transplantation (HSCT). Important causes of diarrhea after HSCT include acute graft-versus-host disease (GVHD), infections, and medications. After the transplantation and engraftment of hematopoietic stem cells from umbilical-cord blood, we observed a new syndrome of culture-negative, antibiotic-responsive diarrhea not attributable to any known cause.

METHODS

We conducted a retrospective cohort study of all patients undergoing cord-blood HSCT at our center between March 2003 and March 2010. The cord colitis syndrome was defined as a persistent diarrheal illness in such patients that was not due to acute GVHD, viral or bacterial infection, or another identifiable cause. Clinical and histopathological features of patients meeting the case definition were further analyzed.

RESULTS

Among 104 patients who underwent cord-blood HSCT at our center, the cord colitis syndrome developed in 11 (10.6%). The 1-year Kaplan–Meier cumulative probability of meeting the case definition for the syndrome was 0.16. The median time to onset after transplantation was 131 days (range, 88 to 314). All patients had a response to a 10-to-14-day course of empirical therapy with metronidazole, alone or in combination with a fluoroquinolone. Five of the 11 patients (45%) had recurrent diarrhea shortly after discontinuation of antibiotics, and all patients who had a relapse had a response to reinitiation of antibiotic therapy. On histologic examination, all patients with the cord colitis syndrome had chronic active colitis, with granulomatous inflammation present in 7 of 11 patients (64%).

CONCLUSIONS

The cord colitis syndrome is clinically and histopathologically distinct from acute GVHD and other causes of diarrhea in patients who have undergone cord-blood HSCT and is relatively common in this patient population. The syndrome should be considered in such patients who have diarrhea that is not attributable to other causes.

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Hematopoietic stem-cell transplantation (HSCT) with the use of umbilical-cord blood is effective in patients for whom a sibling or matched, unrelated donor is not available.[1-4] Acute graft-versus-host disease (GVHD), a major cause of illness in patients undergoing HSCT, is less severe with cord-blood transplants than with adult donor transplants.[1-5] However, cord-blood HSCT is associated with an increased risk of infection related to delayed immune reconstitution because of the infusion of naive immune cells with the graft.[6-9]

Acute GVHD and gastrointestinal infection are important causes of diarrhea after HSCT.[10,11] Distinguishing between them is important because their treatment differs considerably: acute GVHD is treated with increased immunosuppression, whereas infection is treated with appropriate antimicrobial therapy. Classic viral causes of diarrhea after transplantation include cytomegalovirus and adenovirus.[12-15] More common gastrointestinal viral pathogens, such as rotavirus and norovirus, are increasingly recognized as frequent causes of diarrhea in patients who have undergone HSCT.[16,17] Epstein–Barr virus (EBV) infection resulting in post-transplantation lymphoproliferative disease that involves the gut may cause diarrhea.[18] Protozoal infections due to giardia and cryptosporidium are possible causes, but the risk of such infections is minimized by the strict hygiene practices used after transplantation.[14,19] Conditioning-related mucositis[20] and neutropenic enterocolitis[21] frequently cause diarrhea before engraftment; *Clostridium difficile*[22] infection and medication-related diarrhea[23,24] are common throughout the transplantation course.

In patients undergoing cord-blood HSCT at our center, we have observed a syndrome of culture-negative, antibiotic-responsive diarrhea after engraftment that is not attributable to any of the aforementioned causes of diarrhea. We report the clinical and epidemiologic characteristics of patients with this gastrointestinal syndrome, which we have termed the cord colitis syndrome.

METHODS

PATIENTS AND STUDY DESIGN

All patients who underwent cord-blood HSCT at the Dana–Farber Cancer Institute/Brigham and Women's Hospital Hematopoietic Stem Cell Transplantation Service between March 1, 2003, and March 31, 2010, were identified through the service's clinical database. A waiver of the requirement for informed consent was granted by the Office for Human Research Studies of Dana–Farber/Harvard Cancer Center, which approved the study.

A total of 104 patients underwent cord-blood HSCT during the study period; 101 patients each received 2 units of cord-blood stem cells, and 3 patients each received 1 unit (Table 1).[5,6] The median follow-up period was 452 days (range, 1 to 2409). Twenty-six patients underwent myeloablative conditioning, typically with cyclophosphamide, total-body irradiation, and fludarabine. Seventy-eight patients underwent reduced-intensity conditioning regimens, most commonly with fludarabine, melphalan, and antithymocyte globulin (the latter at a dose of 6 mg per kilogram of body weight). Sirolimus–tacrolimus (71 patients), cyclosporine–mycophenolate mofetil (15), tacrolimus–mycophenolate mofetil (13), or a combination of these medications with either methotrexate (in 5 patients) or glucocorticoids (in 9) were used for GVHD prophylaxis.[5,6,25] With the exception of methotrexate, individual drugs used for GVHD prophylaxis were started during the conditioning regimen, tapered starting between day 60 and day 100 after transplantation, and discontinued by day 180 unless GVHD occurred. Patients were treated according to single-group protocols, or the conditioning regimen and GVHD prophylaxis were chosen at the discretion of the treating physician.[5,6]

Data on covariates of interest were identified through the transplantation service's clinical database and the Partners HealthCare System Research Patient Data Repository. Covariates included age, sex, self-reported race, primary disease that necessitated HSCT, date of HSCT, incident acute GVHD and date of diagnosis, organ-specific stage and acute GVHD grade (according to the consensus scale for grading the clinical severity of GVHD[26]), and date of death or last clinic visit on or before August 1, 2010.

Medical records of all patients who underwent cord-blood HSCT were reviewed for all episodes of diarrheal illness after engraftment. Data collected included patients' or clinicians' reports of the quality of stool, duration of illness, weight loss, need for hospitalization, results of microbiologic testing of stool and intestinal-biopsy specimens, results of abdominal imaging, reported gross appearance of mucosa and histopathological features of endoscopic gastrointestinal-biopsy samples, type and duration of antimicrobial treatment, response to

Table 1. Baseline Characteristics of the Entire Cohort and of Patients with and Those without the Cord Colitis Syndrome (CCS).*

Characteristic	Total	CCS	No CCS	P Value
No. of patients — no. (%)	104 (100)	11 (10.6)	93 (89.4)	
Male sex — no. (%)	57 (54.8)	5 (45.5)	52 (55.9)	0.54
White race — no. (%)†	86 (82.7)	9 (81.8)	77 (82.8)	1.00
Median age (range) — yr	48 (19–67)	40 (28–59)	49 (19–67)	0.30
Alive at censoring of data — no. (%)	47 (45.2)	8 (72.7)	39 (41.9)	0.06
Underlying disease — no. (%)				0.9
Acute myeloid leukemia	36 (34.6)	3 (27.3)	33 (35.5)	
Acute lymphoblastic leukemia	7 (6.7)	1 (9.1)	6 (6.5)	
Chronic lymphocytic leukemia	5 (4.8)	1 (9.1)	4 (4.3)	
Chronic myeloid leukemia	5 (4.8)	1 (9.1)	4 (4.3)	
Myelodysplastic syndrome	10 (9.6)	1 (9.1)	9 (9.7)	
Non-Hodgkin's lymphoma	23 (22.1)	2 (18.2)	21 (22.6)	
Hodgkin's disease	8 (7.7)	1 (9.1)	7 (7.5)	
Aplastic anemia	7 (6.7)	1 (9.1)	6 (6.5)	
Myeloproliferative disorder	3 (2.9)	0	3 (3.2)	
Conditioning regimen — no. (%)				0.46
Reduced-intensity conditioning	78 (75.0)	7 (63.6)	71 (76.3)	
Melphalan–fludarabine–ATG	59 (56.7)	4 (36.4)	55 (59.1)	
Other	19 (18.3)	3 (27.3)	16 (17.2)	
Ablative	26 (25.0)	4 (36.4)	22 (23.7)	
Cyclophosphamide–TBI–fludarabine	18 (17.3)	3 (27.3)	15 (16.1)	
Other	8 (7.7)	1 (9.1)	7 (7.5)	
GVHD prophylaxis — no. (%)				
Tacrolimus–sirolimus	71 (68.3)	9 (81.8)	62 (66.7)	0.5
Tacrolimus–mycophenolate mofetil	13 (12.5)	0	13 (14.0)	0.35
Cyclosporine–mycophenolate mofetil	15 (14.4)	2 (18.2)	13 (14.0)	0.66
Methotrexate, any	5 (4.8)	1 (9.1)	4 (4.3)	0.43
Glucocorticoids, any	9 (8.7)	2 (18.2)	7 (7.5)	0.24
Acute GVHD grade — no. (%)‡				
≥2	21 (20.2)	5 (45.5)	16 (17.2)	0.04
≥1	34 (32.7)	6 (54.5)	28 (30.1)	0.17

* ATG denotes antithymocyte globulin, GVHD graft-versus-host disease, and TBI total-body irradiation.
† Race was determined by self-report.
‡ According to the consensus scale for grading the clinical severity of acute GVHD, 0 indicates no GVHD and 1 through 4 indicate increasing GVHD severity on the basis of organ-specific manifestations.[26]

treatment, and relapse of diarrheal illness after treatment.

CASE DEFINITION

The cord colitis syndrome was defined as a persistent diarrheal illness (duration, >7 days) in a patient undergoing cord-blood HSCT that was not caused by acute GVHD, bacterial (including *C. difficile*) or viral infection, post-transplantation lymphoproliferative disease, or another identifiable cause on microbiologic and histopathological examination.

HISTOPATHOLOGICAL REVIEW

Cases of the cord colitis syndrome with available endoscopic mucosal-biopsy material (as detailed in

the Results section) were retrieved from the surgical-pathology files. Material included hematoxylin-and-eosin–stained slides and, in several cases, histochemical, immunohistochemical, and in situ hybridization studies conducted during the diagnostic workup. All material was reviewed by two gastrointestinal pathologists who were unaware of the patients' clinical characteristics. A detailed morphologic evaluation was conducted, with cases assessed for the presence or absence of the following histologic features: basal plasmacytosis, Paneth-cell metaplasia, architectural distortion, granulomas, surface epithelial injury, and viral cytopathic effect. When granulomas were present, they were characterized as associated with crypt rupture, loose, or epithelioid (as in Crohn's disease). Inflammatory activity was assessed and graded as follows: none (no appreciable neutrophilia), focal (rare cryptitis), mild (cryptitis), moderate (crypt abscesses), or severe (ulceration). GVHD features evaluated included crypt epithelial apoptosis and crypt loss; these were graded from 0 to 4 according to published criteria.[27]

On the basis of colon-biopsy findings, the overall pattern of morphologic injury was classified as GVHD-like, active colitis, chronic active colitis, or chronic inactive colitis. For this assessment, cases were considered GVHD-like if they were characterized by an apoptotic colonopathy without appreciable inflammatory activity or features of chronicity. Basal plasmacytosis, Paneth-cell metaplasia, architectural distortion, and granulomas were considered features of chronicity.

In addition, all reports on gastrointestinal biopsies in patients who underwent allogeneic HSCT with the use of stem cells from adult (related or unrelated) donors during the study period were reviewed. We identified patients whose reports contained one or more of the following terms: "granuloma," "Paneth cell," and "active colitis." Medical records and histologic sections were further reviewed to assess whether a clinical pattern similar to that of the cord colitis syndrome was present.

STATISTICAL ANALYSIS

The statistical analysis was designed to determine whether the cord colitis syndrome was associated with any characteristics of the cord-blood HSCT cohort. Only patients who met the case definition of the syndrome and had compatible histopathological findings were included in the analysis. We compared baseline characteristics and covariates of interest between patients with and those without the cord colitis syndrome, using a two-sided Fisher's exact test or Wilcoxon rank-sum test as appropriate. Kaplan–Meier curves were calculated to determine the cumulative probability of the development of the syndrome. Statistical analysis was performed with the use of SAS software, version 9.1 (SAS Institute).

RESULTS

CLINICAL CHARACTERISTICS OF THE CORD COLITIS SYNDROME

Eleven of 104 patients (10.6%) met the criteria for the cord colitis syndrome. An additional patient had relapsing antibiotic-responsive diarrhea that was compatible with the syndrome but did not undergo endoscopic biopsy and was therefore not included in the analysis. The 1-year cumulative probability of meeting the case definition for the cord colitis syndrome was 0.16. The median time to onset of the syndrome was 131 days (range, 88 to 314) after cord-blood HSCT. Most commonly, patients reported that stools were watery (82%) and nonbloody (91%), and they were often associated with fever (64%). The median duration of diarrhea before colonoscopy was 18 days (range, 5 to 59). Nearly all patients (91%) with the cord colitis syndrome had lost weight as compared with their preillness weight (median loss, 2.3 kg; range, 0 to 10.9). Eight patients (73%) with the syndrome required hospitalization. There was no clustering of cases or seasonal variation over time (Table 2).

MICROBIOLOGIC FINDINGS

Clinically driven microbiologic evaluations during episodes of the cord colitis syndrome were performed at the discretion of the treating physicians. Evaluations included stool *C. difficile* toxin assays; bacterial, viral, and fungal cultures; and testing for protozoa and parasites. Tests were performed for a variety of organisms, including cytomegalovirus, adenovirus, herpes simplex virus (HSV), varicella–zoster virus, salmonella, shigella, aeromonas, plesiomonas, campylobacter, yersinia, cryptosporidia, and microsporidia. All tests performed in all 11 patients were negative. Details of all microbiologic testing performed are presented in Tables S1 and S2 of the Supplementary Appendix, available with the full text of this article at NEJM.org.

Table 2. Clinical Characteristics of Patients with the Cord Colitis Syndrome.*

Patient No.	Symptoms				Hospitalization	Imaging‡			Mucosal Appearance on Biopsy				Treatment					
	Fever	Watery BM	Bloody BM	Weight Loss†		Colonic-Wall Thickening	Focal	Diffuse	Erythema	Edema	Ulceration	Hemorrhagic	FQ	Metro	Response	Initial Treatment Duration	Relapse	Relapse Treatment Duration
				kg												*days*		*days*
1	Yes	Yes	No	3.2	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	14	No	NA
2	Yes	Yes	No	10.9	Yes	No	No	No	No	No	No	No	Yes	Yes	Yes	10	Yes	14
3	Yes	Yes	No	5.6	Yes	—	—	—	Yes	Yes	No	No	Yes	Yes	Yes	21	No	NA
4	Yes	Yes	No	2.0	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	10	Yes	730
5	Yes	Yes	No	1.5	Yes	—	—	—	Yes	No	No	No	Yes	Yes	Yes	90	Yes	—§
6	No	No	No	8.4	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	14	No	NA
7	No	Yes	No	2.1	No	—	—	—	Yes	No	No	Yes	Yes	Yes	Yes	14	Yes	360
8	Yes	Yes	No	6.5	Yes	—	—	—	Yes	Yes	No	No	Yes	Yes	Yes	45	No	NA
9	No	Yes	Yes	1.2	No	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	10	No	NA
10	No	No	No	0	No	Yes	Yes	No	No	Yes	No	No	No	Yes	Yes	14	No	NA
11	Yes	Yes	No	2.3	Yes	—	—	—	Yes	Yes	Yes	No	Yes	Yes	Yes	60	Yes	60
Total patients — no. (%)	7 (64)	9 (82)	1 (9)	10 (91)	8 (73)	5 (83)	3 (50)	2 (33)	9 (82)	5 (45)	4 (36)	1 (9)	9 (82)	11 (100)	11 (100)		5 (45)	

* BM denotes bowel movement, FQ fluoroquinolone, Metro metronidazole, and NA not applicable.
† The median weight loss was 2.3 kg.
‡ Imaging was not performed in five patients.
§ Patient 5 had received 90 days of therapy and was still being treated for a relapse when data were censored.

IMAGING

Six patients underwent abdominal computed tomography (CT) as part of the evaluation for diarrhea. Five patients (83%) had evidence of colonic-wall thickening, including two patients (33%) with diffuse colonic involvement, two (33%) with sigmoid thickening, and one (17%) with thickening of the cecum and ascending colon (Table 2).

HISTOPATHOLOGICAL FINDINGS AND GROSS MUCOSAL APPEARANCE

All 11 patients with the cord colitis syndrome underwent diagnostic colonoscopy with biopsy at the time of presentation. On inspection, 9 patients (82%) had mucosal erythema, 5 (45%) had edematous mucosa, and 4 (36%) had mucosal ulcerations. Only 1 patient had hemorrhagic mucosa; no patients had pseudomembranes.

Thirty-seven biopsy specimens from the 11 patients were reviewed. The degree of inflammatory activity ranged from none to severe. Basal plasmacytosis was not a prominent feature, identified in only 1 biopsy specimen from 1 patient. In single biopsy specimens from 4 other patients, crypts were lifted off the muscularis mucosae by a mixed inflammatory infiltrate with numerous histiocytes. Paneth-cell metaplasia was present in biopsy specimens of the left colon (distal to the splenic flexure) from 8 of the 11 patients (73%). Pyloric metaplasia (indicative of chronic ileitis) was present in 1 of 2 patients who underwent biopsy of the terminal ileum. Substantial architectural distortion was noted in only 1 patient. Surface epithelial injury was noted in 7 of the 11 patients, always in the colon. A viral cytopathic effect was identified in 1 patient (Patient 11) with prior cytomegalovirus infection, though only rare cytomegalovirus-infected cells were detected in the lamina propria by immunohistochemical analysis. Three months before the onset of the cord colitis syndrome, the patient had had cytomegalovirus colitis, which had resolved before his presentation with the syndrome. No viral cytopathic effect was seen in other biopsy specimens.

Granulomas were present in 7 of 11 patients (64%), noted in 15 biopsy specimens of the stomach, duodenum, and colon. Five biopsy specimens showed tight, epithelioid granulomas, whereas granulomas associated with crypt or gland rupture and ill-defined lymphohistiocytic aggregates were seen in 6 and 8 specimens, respectively (some biopsy specimens had more than 1 type of granuloma). Although it was not a prominent histologic feature, mildly increased crypt or gland epithelial apoptosis was present in 8 of 11 patients (73%). Except for the single positive immunostaining study for cytomegalovirus, noted above, all special studies for microorganisms were negative, including Gram's stain; stains for acid-fast bacilli, cytomegalovirus, HSV types 1 and 2, adenovirus, and varicella–zoster virus; methenamine silver stain, Giemsa stain, in situ hybridization for EBV-encoded RNA, and helicobacter stain (Table 3, and Table S2 of the Supplementary Appendix).

Biopsy specimens from all 11 patients showed chronic active colitis, often with granulomas of various types. No patient had active colitis without features of chronicity (Fig. 1 and Table 3).

HISTOPATHOLOGICAL FINDINGS IN OTHER ALLOGENEIC TRANSPLANT RECIPIENTS

An additional 1261 patients underwent allogeneic peripheral-blood or bone marrow HSCT during the study period. A total of 381 patients underwent 609 gastrointestinal endoscopy and biopsy procedures. Only 1 patient had findings suggestive of the chronic active, granulomatous colitis observed in the patients with the cord colitis syndrome. On further review, more prominent chronic inflammation of the lamina propria and tissue eosinophils were noted. The patient had intermittent diarrhea and peripheral-blood eosinophilia that resolved with immunosuppressive therapy; antibiotic therapy was not required. Thus, the clinical course in this patient was distinct from that in patients who underwent cord-blood HSCT.

TREATMENT

Once other causes of diarrhea were ruled out, all patients received a 10-to-14-day course of antibacterial agents at the discretion of the treating physicians. Nine patients were treated with metronidazole and a fluoroquinolone, including five with ciprofloxacin and four with levofloxacin. Two patients were treated with metronidazole alone. All patients had a clinical response to antibacterial treatment, with a clinically significant reduction in stool frequency or resolution of diarrhea after a median of 5 days (range, 3 to 14). Treatment was continued until symptoms resolved, with a median treatment duration of 14 days (range, 10 to 90). Four patients received initial courses of treatment that were longer than 14 days (range, 21 to 90) because of mild persistent symptoms or difficulty

Table 3. Pathological Characteristics of Patients with the Cord Colitis Syndrome.*

Patient No.	Biopsy Location	Inflammatory Activity	Paneth-Cell Metaplasia	Granulomas	Apoptosis Grade†	Mucosal Surface Injury	Special Stains
1	Sigmoid colon	Mild	Yes	No	1	Yes	None
2	Rectosigmoid colon	Mild	Yes	Yes	1	Yes	None
3	Sigmoid colon	Moderate	No	Yes	0–1	No	None
4	Sigmoid colon	Moderate to severe	Yes	Yes	1	Yes	AFB, PAS-D, Giemsa, MSS, CMV, HSV-1 and HSV-2, Ad
5	Sigmoid colon	Mild	Yes	Yes	1	Yes	AFB, CMV, EBER, HP
6	Sigmoid colon	Mild	Yes	No	1	Yes	AFB, MSS, VZV, HSV-1 and HSV-2, Ad, CMV, EBER
7	Sigmoid colon	Mild	No	Yes	1	No	AFB, MSS, Gram's, CMV, Alcian yellow
8	Rectum	Focal	No	Yes	2	Yes	AFB, MSS, Gram's, PAS-D, Alcian yellow
9	Sigmoid colon	Mild	Yes	No	1	No	CMV
10	Sigmoid colon	Focal	Yes	Yes	0–1	No	AFB, MSS, trichrome
11	Sigmoid colon	Moderate to severe	Yes	No	0–1	Yes	CMV (positive), MSS

* Staining with Alcian yellow was performed on specimens from separate biopsies of the stomach. Ad denotes immunohistochemical stain for adenovirus, AFB special stain for acid-fast bacilli, CMV immunohistochemical stain for cytomegalovirus, EBER in situ hybridization for Epstein–Barr virus–encoded RNA, HP immunohistochemical stain for helicobacter (from separate gastric biopsy specimens), HSV-1 and HSV-2 immunohistochemical stain for herpes simplex virus types 1 and 2, MSS methenamine silver stain, PAS-D periodic acid–Schiff with diastase, and VZV immunohistochemical stain for varicella–zoster virus.

† Histopathological gastrointestinal graft-versus-host disease criteria were used for grading. Grades range from 0 to 4, with 0 indicating no appreciable apoptosis, 1 increased crypt epithelial apoptosis, 2 loss of individual crypts, 3 loss of two or more contiguous crypts, and 4 subtotal or total crypt loss.[27]

gaining weight. Five patients (45%) had recurrent diarrhea a median of 7 days (range, 4 to 60) after discontinuation of antibiotics. The five patients who had a relapse were re-treated with several maintenance courses of fluoroquinolone and metronidazole for a median of 120 days (range, 14 to 730), with resolution of the diarrhea in all five. Symptoms were generally well controlled while the patients received therapy; treatment continued until withdrawing antibacterial agents did not result in a return of symptoms. There were no incident episodes of *C. difficile* colitis or tendinitis.

COVARIATE ANALYSIS

No association was noted between the occurrence of the cord colitis syndrome and age, race, the primary hematologic disease, or the conditioning regimen or GVHD prophylactic regimen used. A higher percentage of patients with the cord colitis syndrome (45.5%) had previously received treatment for grade 2 or higher acute GVHD, as compared with the cohort (17.2%; P=0.04), without organ-specific predominance; only one patient had prior acute gastrointestinal GVHD (Table 1). All patients with the cord colitis syndrome and acute GVHD had resolution of GVHD before the syndrome developed; the median time from acute GVHD to diagnosis of the cord colitis syndrome was 184 days (range, 105 to 328).

DISCUSSION

We observed a syndrome of antibiotic-responsive, culture-negative diarrhea occurring after cord-blood HSCT, which we have termed the cord colitis syndrome. Because of the high incidence of acute GVHD after HSCT and the similar initial presentation of the two syndromes, it is important to distinguish the cord colitis syndrome from GVHD.

Patients with the cord colitis syndrome have persistent watery, nonbloody diarrhea that is often associated with weight loss and frequently re-

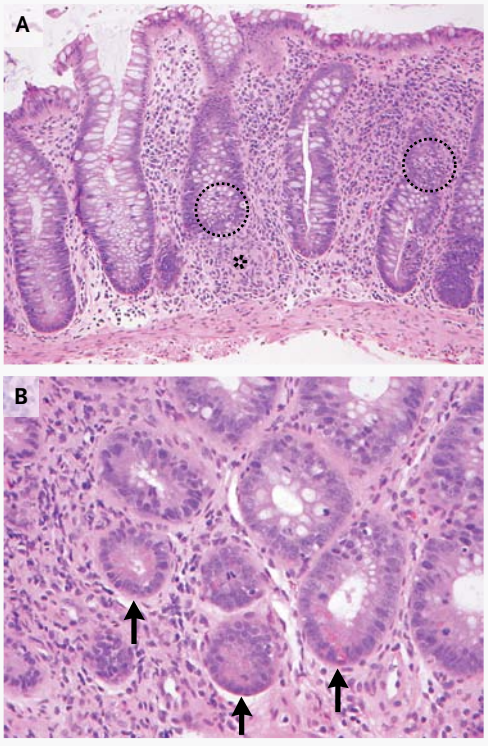

Figure 1. Histologic Features of the Cord Colitis Syndrome (Hematoxylin and Eosin).

Panel A shows prominent granulomatous inflammation (asterisk), neutrophilic cryptitis (circles), and mild crypt epithelial apoptosis; Panel B shows Paneth-cell metaplasia (arrows).

quires hospitalization. Abdominal CT imaging generally reveals focal or diffuse colonic-wall thickening that is radiographically consistent with colitis. Colonoscopy in these patients commonly reveals erythematous mucosa on gross inspection.

The main feature distinguishing the cord colitis syndrome from acute GVHD is the histopathological finding of chronic active colitis associated with granulomas. The histologic hallmark of acute GVHD in the gastrointestinal tract is increased apoptosis.[27] In colon-biopsy specimens, this finding predominates in crypt bases. Higher-grade lesions are also associated with increasing degrees of crypt loss (Fig. 2). Acute GVHD is not characterized by increased plasmacytic inflammation in the lamina propria, neutrophilic infiltration of the epithelium, Paneth-cell metaplasia, or granuloma formation.

The histologic features of chronic gastrointestinal GVHD are not well characterized. The disease tends to affect the oral mucosa and esophagus and to spare the small and large intestines. In cases of intestinal involvement, submucosal fibrosis with mucosal sparing has been described.[28,29] Chronic mucosal injury in patients with GVHD has been described in a single case series.[30] The patients had prominent architectural distortion and a hypocellular lamina propria. One of five patients in the case series had focal inflammatory activity. Although the histologic pattern of injury described in one case series may represent chronic GVHD, alternative explanations (e.g., drugs and infections) are possible.[30]

The histologic findings in patients with the cord colitis syndrome are distinct from those in patients with acute or chronic GVHD. The presence of neutrophilic infiltration superimposed on Paneth-cell metaplasia suggests chronic and ongoing injury. Although crypt epithelial apoptosis was observed, it was much less prominent than that typically observed in acute GVHD. In addition, although there was evidence of chronic mucosal injury in the form of Paneth-cell metaplasia in our patients, the architectural distortion characteristic of the patients in the series reported by Asplund and Gramlich[30] was not observed, and our patients had more pronounced inflammatory activity. The granulomatous inflammation is etiologically nonspecific.

The other distinguishing feature of the cord colitis syndrome is the rapid response to antibacterial treatment, usually with a fluoroquinolone and metronidazole. Relapse is common after the discontinuation of antibacterial agents and may require prolonged treatment courses. In contrast, patients with acute or chronic GVHD have a response to increased immunosuppression. Three patients who received a diagnosis of the cord colitis syndrome were initially treated with both antibiotics and glucocorticoids on admission to the hospital. When it became apparent that their illnesses were not consistent with GVHD, the glucocorticoids were stopped and the antibacterial agents were continued. None of these patients required the reintroduction of immunosuppressive agents. The risks of prolonged antibiotic therapy, including promotion of antimicrobial resistance, must be weighed against the benefits of treating the cord colitis syndrome effectively. Diarrhea, weight loss, and other features of the syndrome greatly affected the quality of life and nutritional status of these patients. The duration of antibac-

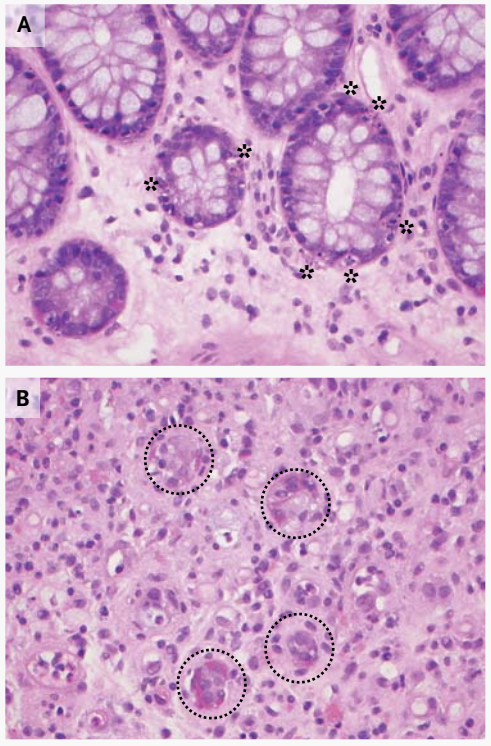

Figure 2. Histologic Features of Acute Gastrointestinal Graft-versus-Host Disease (Hematoxylin and Eosin).

Panel A shows striking crypt epithelial apoptosis (asterisks); Panel B shows total crypt loss with aggregation of endocrine cells (circles).

terial regimens should be tailored to the clinical response.

In our cohort, the cord colitis syndrome was not associated with demographic characteristics, the primary hematologic disease, or the conditioning regimen or GVHD prophylactic regimen. The syndrome was not associated with increased mortality among patients undergoing cord-blood HSCT. A considerable proportion of patients at our center received sirolimus and tacrolimus for GVHD prophylaxis; however, the cord colitis syndrome was identified in patients who did not receive either agent. Patients with a history of grade 2 or higher acute GVHD were more likely to have the cord colitis syndrome than were patients with grade 1 GVHD or no GVHD. In all the patients with GVHD who had the cord colitis syndrome, the GVHD resolved clinically before the syndrome developed. However, the number of patients in the cohort who had had acute GVHD was small, so it is difficult to interpret the importance of this observation. We did not identify a syndrome consistent with the cord colitis syndrome in any of the 1261 patients who underwent non–cord-blood HSCT during the study period.

The cord colitis syndrome responds to antibacterial therapy, which suggests an infectious, possibly bacterial, cause. However, the chronic granulomatous colitis observed on histopathological examination could represent an inflammatory colitis. The histopathological findings observed in the cord colitis syndrome are similar to those seen in Crohn's disease.[31,32] There is evidence that antibiotics may be a useful adjunctive therapy in patients with Crohn's disease.[33,34] A greater understanding of the cord colitis syndrome may provide insights into the pathophysiology of Crohn's disease.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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